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NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)

(PCT Rule 44bis.1(c))

To:

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ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

30 March 2006 (30.03.2006)

Applicant's or agent's file reference

2345.2058002

IMPORTANT NOTICE

International application No.

PCT/US2004/030699

International filing date (day/month/year)

17 September 2004 (17.09.2004)

Priority date (day/month/year)

19 September 2003 (19.09.2003)

Applicant

DECODE GENETICS EHF. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

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HAMILTON, BROOK
SMITH & REYNOLDS, P.C.The International Bureau of WIPO
34, chemin des Colombettes
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C57

ATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 2345.2058002	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2004/030699	International filing date (<i>day/month/year</i>) 17 September 2004 (17.09.2004)	Priority date (<i>day/month/year</i>) 19 September 2003 (19.09.2003)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant DECODE GENETICS EHF.			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> Box No. I | Basis of the report |
| <input checked="" type="checkbox"/> Box No. II | Priority |
| <input checked="" type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input checked="" type="checkbox"/> Box No. VI | Certain documents cited |
| <input checked="" type="checkbox"/> Box No. VII | Certain defects in the international application. |
| <input checked="" type="checkbox"/> Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Date of issuance of this report 21 March 2006 (21.03.2006)
	Authorized officer Philippe Becamel Telephone No. +41 22 338 70 90

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2004/030699International filing date (day/month/year)
17.09.2004Priority date (day/month/year)
19.09.2003International Patent Classification (IPC) or both national classification and IPC
C12Q1/68Applicant
DECODE GENETICS EHF.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US2004/030699

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the International application as filed.
☐ filed together with the international application in computer readable form.
☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43**bis**.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43**bis**.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/030699

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 1-13,31-40,56,58 (N, IS, IA)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☒ the claims, or said claims Nos. 1-13,31-40,56,58 (N, IS, IA) are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. -
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|------------------------------------------------------------|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☒ See separate sheet for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US2004/030699

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	44-55,60-63
	No: Claims	14-30,41-43,57,59
Inventive step (IS)	Yes: Claims	44-55,60-63
	No: Claims	14-30,41-43,57,59
Industrial applicability (IA)	Yes: Claims	14-30,41-55,57,59,60-63
	No: Claims	-

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2004/030699

1 Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.1 The subject-matter of independent claim 1 does not meet the requirements of Article 5 PCT for the following reasons:

1.1.1 It has only been shown that a number of subjects suffering from psychiatric and/or comorbid disorders present an inversion of chromosome 8p23. Experimental evidence for a direct role of the inv8p23 genomic region in the development of psychiatric disorders is missing. From the prior art, it appears that this inversion can be linked to a number of diseases (cf. D1, D2, D3 and D4, Tab.1), but that not all carriers are suffering from said diseases nor from psychiatric disorders (cf. D2, p.241, D4, Tab.1). It has furthermore not been shown, that this inversion can be used to diagnose such disorders. **It even appears not to be possible to diagnose a psychiatric or comorbid disorder by simply analysing the orientation of inv8p23, as a number of carriers of this inversion appear to be healthy, i.e. the parent of the child, wherein the parent carrying the inv8p23 is asymptomatic, while the child showing a variety of symptoms is bearing an additional duplication of the inv8p23 region (cf. D2, p.241, D4, Tab.1).**

1.1.2 Therefore the subject-matter of independent claim 1 and dependent claims 2 to 13, 31 to 40, 56 and 58 does not fulfil the requirements of Article 5 PCT. consequently no examination will be carried out on the subject-matter of said claims.

2 Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are referred to in this communication:

NOVELTY (Article 33(2) PCT)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/030699

- 2.1 D1 discloses ten BAC DNA probes for detecting the orientation of the Inv8p23 genomic region and a method for determining the orientation of the Inv8p23 inversion fragment using said probes (cf. D1, abstract).
D2 discloses a complete physical map and chromosomal markers of the Inv8p23 region and a method for determining the orientation of the Inv8p23 inversion fragment using said markers (cf. D2, p.239 to 240 and p.242 to 243).
D5 and D6 disclose chromosomal markers for detecting the orientation of the Inv8p23 genomic region (cf. D5, p.225, col.1, D6, p.569 and Tab.1 and 2).
Therefore, the subject-matter of **independent claims 14 and 41 is not novel** over D1, D2, D5 and D6 (Article 33(2) PCT).

INVENTIVE STEP (Article 33(3) PCT)

- 2.2 Independent claim 44:
Document D7 is considered to represent the most relevant state of the art for claim 44 in its present form. D7 discloses a method of predicting the efficacy of a drug or treating a psychiatric disorder in a human patient, comprising determining the presence or absence of at least one variance in a gene (cf. cl.108).
- 2.3 The subject-matter of claim 44 differs from the subject-matter disclosed in closest prior art document D7 in that the orientation of the Inv8p23 genomic region is determined, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.
- 2.4 No unexpected technical effect appears to be associated with said difference.
- 2.5 The technical problem to be solved may therefore be regarded as providing an alternative genetic indicator for the efficacy of a drug for treating a psychiatric disorder. The proposed solution is to determine the orientation of the Inv8p23 genomic region, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.
- 2.6 This solution can be considered as involving an inventive step for the following

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/030699

reasons:

- 2.6.1 Even though a link between the 8p23 region and psychiatric disorders is well-known in the state of the art (cf. D1 to D6) and furthermore a link between the Inv8p23 inversion and mental retardation is known (cf. D1 and D3), so far no relationship has been established between the orientation of the inv8p23 genomic region and the efficacy of a drug for treating a psychiatric disorder.
- 2.7 Hence, the subject-matter of **independent claim 44 does involve an inventive step** (Article 33(3) PCT).
- 2.8 Dependent claims 15 to 30, 42, 43, 57 and 59 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, as all of the additional features fall within the scope of routine laboratory practise.

3 Re Item VI**Certain documents cited**

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2005/002419	13.01.2005	17.06.2004	26.06.2003

Non-written disclosures

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
poster	04-08/11/2003	00/11/2003

THORGEIRSSON T E ET AL: "Markers associated with the inversion polymorphism

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/030699

on chromosome 8p23 are associated with Panic Disorders." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 73, no. 5, November 2003 (2003-11), page 514, XP002343054 53RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HUMAN GENETICS; LOS ANGELES, CA, USA; NOVEMBER 04-08, 2003 ISSN: 0002-9297

4 Re Item VII

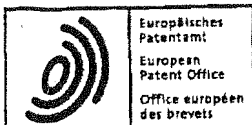
Certain defects in the international application

- 4.1 The numbering of the claims does not comply with Rule 6.1(e) PCT in that some claims are numbered with non-arabic numerals, i.e. claims 13b, 26b, 34b and 43b and some claim numbers are duplicated, i.e. claims with the number 42 to 45 occur twice (Rule 6.1(b) PCT).
Claims 13b, 26b, 34b and 43b were renumbered as claims 56, 57, 58 and 59 respectively and the later claims 42 to 45 were renumbered as claims 60 to 63.

5 Re Item VIII

Certain observations on the international application

- 5.1 Dependent claims 46 to 48 and 60 to 62 appear to refer back to the wrong claims as these claims are defining a method for predicting the efficacy of a drug but are referring back to claim 40, defining a method of diagnosis and claim 41, defining a method of determining the orientation of Inv8p23 respectively (Article 6 PCT).



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24 APR. 2009

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Application No. 04 809 772.9 - 1222	Ref. P 5541 EPPC	Date 17.04.2009
Applicant Decode Genetics EHF.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).



Bruma, Anja
Primary Examiner
For the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents:**

Description, Pages

1, 2, 6-20, 22-30, 33- as published
98

3, 3a, 4, 5, 21, 31, 32, filed with telefax on 20.12.2007
99

Claims, Numbers

1-42 filed with telefax on 20.12.2007

Drawings, Sheets

1-90 as published

Reference can be made to the following communications and letters: official communications of 11.09.2006 (C1), 10.08.2007 (C2) and 18.12.2007 (C3, minutes of telephone conversation) and applicants' letter of reply dated 21.03.2007 (L1), and 20.12.2007 (L2).

After careful consideration of the amendments the examining division takes the following point of view:

1 AMENDMENTS (Article 123(2) EPC)

1.1 The submitted amendments of claims 1-42 comply with the requirements of Article 123(2) EPC.

2 DISCLOSURE, SUPPORT AND CLARITY (Article 83 and Article 84 EPC)

- 2.1 Dependent claims 6,12,28,38 and 39 refer to methods using "markers in linkage disequilibrium with one or more markers..." This formulation renders the subject-matter of said claims unclear as it is not possible to say which polymorphic marker is in said disequilibrium. Thus claims 6,12,28,38 and 39 lack clarity (Art. 84 EPC).
- 2.2 The kit as defined in claim 14 is fundamentally unclear, as no functional features are provided in the claim. The kit is described as comprising at least one polymorphic marker useful for detecting the orientation of the Inv8p23 genomic region, wherein a particular allele of the at least one polymorphic marker is indicative of a particular orientation of Inv8p23, and wherein the orientation of the Inv8p23 genomic region is indicative of the psychiatric disorder. The unclarity arises due to the fact that a marker is defining only a piece of information and not a functional feature. A kit must however be defined by its components, all of them identified by their composition or structural features, in order to be not only clear and supported (Art.84 EPC), but also fully disclosed (Art. 83 EPC).
- 2.3 Furthermore, claims 7,10,12,19,22,24,27,28 are fundamentally unclear, as the markers SG08S517 and DG00AAHB6 they are referring to, are neither defined in the application as filed, nor known in the prior art. The person skilled in the art is therefore at a total loss as to what sequence these markers are referring to (Art.84 EPC). This objection could be overcome by deleting said markers from the claims.
- 2.4 The application provides, in Ex. 5 and 6, results of studies of a possible association between surrogate marker alleles of Inv8p23 orientation and drug response. 150 patients suffering from psychiatric disorders, namely anxiety disorders or depression, and who were treated with either SNRI or SSRI drugs were analysed. The patients were genotyped, after being treated with the drugs at stable doses for at least 4 weeks. From the results of the association studies, it appears that only very few of the markers are significant to predict drug response. The p-values given are not statistically significant for most markers tested. Only marker SG08S71 and SG08S73 appear to be significant for the prediction of the response to combined SNRI and SSRIs and SG08S73 for citalopram and escitalopram response. So it appears that not all markers for the orientation of Inv8p23 solve the problem posed. Furthermore, the results provided are unclear, as for example it is not explained how the relative

risk was assessed, neither is it evident from the figures, what the results of the second table are referring too. Furthermore, as all the data provided is obtained from people suffering either from anxiety disorders or depression, support can neither be found for psychiatric disorders in general, nor for comorbid disorders (Art.84 EPC). Hence, claim 30 lacks support according to Article 84 EPC.

- 2.5 In case the applicant could provide explanations and/or additional data demonstrating an association of these markers and response to the drugs used, the examining division would be willing to acknowledge an inventive step for claim 30, restricted to a method of predicting the efficacy of a drug for treating an anxiety disorders or depression (cf. item 3.9-3.12 of C2).

3 NOVELTY (Article 54 EPC)

- 3.1 Claim 26 does not meet the requirements of novelty as set forth in Article 54 EPC, as the determination of the orientation of Inv8p23 inversion fragment, as defined in D2 or D6 is in deed a method of determining the orientation of the Inv8p23 inversion fragment comprising detecting one polymorphic markers, namely the Inv8p23, as it is a polymorphic marker itself.
Therefore, the subject-matter of claim 26 is not novel over D2 and D6 (Article 54 EPC).

4 INVENTIVE STEP (ARTICLE 56 EPC)

- 4.1 Document D7 is considered to represent the most relevant state of the art for claim 1 in its present form. D7 discloses a method of diagnosing a susceptibility to a psychiatric disorder in an individual comprising detecting a translocation in 8p23(cf. D7, Tab.1).
- 4.2 The subject-matter of claim 1 differs from the subject-matter disclosed in closest prior art document D1 in that the orientation of the Inv8p23 genomic region is determined, wherein the orientation of the Inv8p23 genomic region is indicative of a psychiatric disorder.

- 4.3 No unexpected technical effect appears to be associated with said difference.
- 4.4 The technical problem to be solved may therefore be regarded as providing an alternative method of diagnosing a susceptibility to a psychiatric disorder. The proposed solution is to determine the orientation of the Inv8p23 genomic region, wherein the orientation of the Inv8p23 genomic region is indicative of susceptibility to a psychiatric disorder.
- 4.5 This solution can be considered as involving an inventive step for the following reasons:
- 4.5.1 Even though a link between the 8p23 region and psychiatric disorders is known in the state of the art (cf. for example D3, the whole document, D4, p.225 or D7, Tab.1) and furthermore a link between the Inv8p23 inversion and mental retardation is known (cf. D1 and D3), so far no relationship has been established between the inversion and the orientation of the Inv8p23 genomic region and the susceptibility to psychiatric disease.
- 4.6 Hence, the subject-matter of independent claim 1 does involve an inventive step (Article 56 EPC).
- 4.7 Neither polymorphic markers in linkage disequilibrium with Inv8p23, nor surrogate markers which could be used to detect the orientation of Inv8p23 have been described so far. Therefore, the subject-matter of dependent claim 27 appears to involve an inventive step (Article 56 EPC).
- 4.8 Document D5 is considered to represent the most relevant state of the art for claim 30 (limited to psychiatric disorders) in its present form. D5 discloses a method of predicting the efficacy of a drug or treating a psychiatric disorder in a human patient, comprising determining the presence or absence of at least one variance in a gene (cf. cl.108).
- 4.9 The subject-matter of claim 30 differs from the subject-matter disclosed in closest prior art document D5 in that the orientation of the Inv8p23 genomic region is determined, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.
- 4.10 No unexpected technical effect appears to be associated with said difference.

4.11 The technical problem to be solved may therefore be regarded as providing an alternative genetic indicator for the efficacy of a drug for treating a psychiatric disorder. The proposed solution is to determine the orientation of the Inv8p23 genomic region, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.

4.12 This solution cannot be considered as involving an inventive step for the following reasons:

4.12.1 From the results of the association studies of drug response to surrogate marker alleles it appears that only very few of the markers are significant to predict drug response, as the p-values given are not statistically significant for most markers tested. Only marker SG08S71 and SG08S73 appear to be significant for the prediction of the response to combined SNRI and SSRIs and SG08S73 for citalopram and escitalopram response. So it appears that not all markers for the orientation of Inv8p23 solve the problem posed (cf. item 2.4 and 2.5 above).

4.12.2 Hence, the subject-matter of independent claim 30 does not involve an inventive step (Article 56 EPC).

5 CONCLUSIONS

5.1 The Applicant is invited to file new claims which take account of the above comments.



ARNASON | FAKTOR

07 JAN. 2008

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Application No. 04 809 772.9 - 1222	Ref. P 5541 EPPC	Date 03.01.2008
Applicant Decode Genetics EHF.		

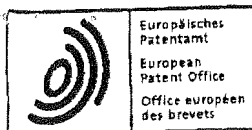
Result of consultation

A copy of the result of consultation of 18.12.2007 is enclosed for your information.



Bruma, Anja
For the Examining Division

Enclosure(s): Copy of result of consultation (Form 2036)



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Application No. :

04 809 772.9

Consultation by telephone with the applicant / representative

Despatch for information

Participants

Applicant: Decode Genetics EHF.
Representative: Sigurður Ingvarsson
Member(s) of the
Examining Division: Bruma, Anja

Result of consultation

The applicant provided arguments regarding the allowability with regards to Article 123(2) EPC of the amendments of claims 8 and 39 filed with the telefax dated 21.03.2007.

claim 8:

The basis for the specific marker combination given in claim 8 provided by the applicant is claim 7.

The examiner upheld the objection with regards to Article 123(2), as claim 7 does not mention the specific marker combination (claim 7 lists a group of 30 markers, which comprise also the markers of the combination defined in claim 8, but does not specify the alleles of said markers).

claim 39:

Claim 39 in its present form refers to a method of predicting the efficacy of a drug, wherein the one and more marker are selected from the group consisting of DG8S269, SG08S95, SG08S5, SG08S71 and SG08S73, and markers in linkage disequilibrium therewith. The examiner argued in the communication dated 10.08.2007, that no basis could be found in the original disclosure for the markers in linkage disequilibrium therewith.

The applicant argued that p.4, l.30 to p.5, l.12 form the basis for said amendment.

The examiner agrees that said pages form the basis for said amendment as said pages refer to the embodiments of the invention in general, i.e. comprising the method of predicting the efficacy of a drug.

Claim 39 in its present form is therefore allowable according to Article 123(2) EPC.

The applicant will take these results into consideration when replying to the communication dated 10.08.2007.



Date 03.01.2008

Sheet 2

Application No.: 04 809 772.9

18.12.2007

.....
Date

Bruma, Anja

.....
Examiner

ANNAD



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Europäisches
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European
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Directorate General 2

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13 AUG. 2007

Received with thanks

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Application No. 04 809 772.9 - 1222	Ref. P 5541 EPPC	Date 10.08.2007
Applicant Decode Genetics EHF.		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 2 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).



Bruma, Anja
Primary Examiner
for the Examining Division

Enclosure(s): 6 page/s reasons (Form 2906)

C55



Beschaid/Protokoll (Anlage)

Communication/Minutes (Annex)

Notification/Procès-verbal (Annexe)

Datum
Date 10.08.2007
Date

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Sheet 1
Feuille

Anmelde-Nr.:
Application No.: 04 809 772.9
Demande n°:

The examination is being carried out on the following application documents:

Description, Pages

1-99 as published

Claims, Numbers

1-42 filed with telefax on 21.03.2007

Drawings, Sheets

1-90 as published

After careful consideration of the amendments and the arguments filed by the applicant with the telefax of 21.03.2007 (L1), the examining division takes the following point of view:

Reference is made to the following document (in addition to D1-D6, introduced in the first communication); the numbering will be adhered to in the rest of the procedure:

D7: MACINTYRE D J ET AL: "Chromosomal abnormalities and mental illness."
MOLECULAR PSYCHIATRY. MAR 2003, vol. 8, no. 3, March 2003 (2003-03), pages 275-287, XP002343058 ISSN: 1359-4184

1 AMENDMENTS (Art. 123(2) EPC)

- 1.1 The amendments filed with L1 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 123(2) EPC. The amendments concerned are the following:



- 1.1.1 Present claim 8 refers to the specific combination of markers comprising the A allele for SG08S71, the C allele for SG08S73 and the G allele for DG00AAHBG. The application as originally filed does not provide any basis for this specific marker combination (cf. Fig.13A and the description, p.4-8, as published).
- 1.1.2 Claim 39 in its present form refers to a method of predicting the efficacy of a drug, wherein the one and more marker are selected from the group consisting of DG8S269, SG08S95, SG08S5, SG08S71 and SG08S73, and markers in linkage disequilibrium therewith. No basis can be found in the original disclosure for the markers in linkage disequilibrium therewith. The Applicant argued that p.4, l.30 to p.5, l.12 form the basis for said amendment. However, pages 4 to 5 refer only to the methods of diagnosing a psychiatric disorder or detecting the orientation of Inv8p23 and not to the method of predicting the efficacy of a drug. By deleting the expression "and markers in linkage disequilibrium therewith" from the claim the requirements of Article 123(2) can be satisfied.

2 NOVELTY (Art. 54 EPC)

- 2.1 The present set of claims appears to be novel over the prior art.

3 INVENTIVE STEP (Art. 56 EPC)

- 3.1 Document D7 is considered to represent the most relevant state of the art for claim 1 in its present form. D7 discloses a method of diagnosing a susceptibility to a psychiatric disorder in an individual comprising detecting a translocation in 8p23 (cf. D7, Tab.1).
- 3.2 The subject-matter of claim 1 differs from the subject-matter disclosed in closest prior art document D1 in that the orientation of the Inv8p23 genomic region is determined, wherein the orientation of the Inv8p23 genomic region is indicative of the a psychiatric disorder.



- 3.3 No unexpected technical effect appears to be associated with said difference.
- 3.4 The technical problem to be solved may therefore be regarded as providing an alternative method of diagnosing a susceptibility to a psychiatric disorder. The proposed solution is to determine the orientation of the Inv8p23 genomic region, wherein the orientation of the Inv8p23 genomic region is indicative susceptibility to a psychiatric disorder.
- 3.5 This solution can be considered as involving an inventive step for the following reasons:
- 3.5.1 Even though a link between the 8p23 region and psychiatric disorders is known in the state of the art (cf. for example D3, the whole document, D4, p.225 or D7, Tab.1) and furthermore a link between the Inv8p23 inversion and mental retardation is known (cf. D1 and D3), so far no relationship has been established between the inversion and the orientation of the Inv8p23 genomic region and the susceptibility to psychiatric disease.
- 3.6 Hence, the subject-matter of **independent claim 1 does involve an inventive step** (Article 56 EPC).
- 3.7 Neither polymorphic markers in linkage disequilibrium with Inv8p23, nor surrogate markers which could be used to detect the orientation of Inv8p23 have been described so far. Therefore, the subject-matter of independent claims 14 and 26 appears to involve an inventive step (Article 56 EPC).
- 3.8 Document D5 is considered to represent the most relevant state of the art for claim 30 in its present form. D5 discloses a method of predicting the efficacy of a drug or treating a psychiatric disorder in a human patient, comprising determining the presence or absence of at least one variance in a gene (cf. cl.108).
- 3.9 The subject-matter of claim 30 differs from the subject-matter disclosed in closest prior art document D5 in that the orientation of the Inv8p23 genomic region is determined, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.



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Date 10.08.2007
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- 3.10 No unexpected technical effect appears to be associated with said difference.
- 3.11 The technical problem to be solved may therefore be regarded as providing an alternative genetic indicator for the efficacy of a drug for treating a psychiatric disorder. The proposed solution is to determine the orientation of the Inv8p23 genomic region, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.
- 3.12 This solution can be considered as involving an inventive step for the following reasons:
- 3.12.1 Even though a link between the 8p23 region and psychiatric disorders is well-known in the state of the art (cf. D1 to D6) and furthermore a link between the Inv8p23 inversion and mental retardation is known (cf. D1 and D3), so far no relationship has been established between the orientation of the Inv8p23 genomic region and the efficacy of a drug for treating a psychiatric disorder.
- 3.13 Hence, the subject-matter of **independent claim 30 does involve an inventive step** (Article 56 EPC).

4 CONCLUSIONS

- 4.1 The Applicant is invited to file new claims which take account of the above comments.
- 4.2 In the reply, the parts of the application, as originally filed, which form the basis for the amendments (cf Art 123(2) EPC) should be **clearly indicated** (page/line numbers etc).
- 4.3 In order to expedite the procedure, the Applicant is kindly asked to **clearly point out where the amendments have been made**, possibly by enclosing a copy of the original pages with the corrections in the manuscript.
- 4.4 The amendments should be filed by way of replacement pages, avoiding



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Date 10.08.2007
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unnecessary recasting of the description. The Applicant should also take account of the requirements of Rule 36(1) EPC. In particular a fair copy of the amendments should be filed. If handwritten amendments are submitted, they should be clearly legible for the printer.

- 4.5 Once an allowable set of claims has been defined, then the Applicant is requested to do the following:
- i) The description should be brought into conformity with the amended claims (Rule 27(1)(c) EPC). Care should be taken during revision not to add subject-matter which extends beyond the content of the application as originally filed (Art 123(2) EPC). Any statements of problems or advantages should be restricted to the letter of reply.
 - ii) Documents **D1-D6** should be identified in the description and the relevant background art disclosed therein should be briefly discussed if the subject-matter for which these documents are relevant prior art remains in the claims (Rule 27(1)(b) EPC).
 - iii) A European patent application should be self contained. Therefore, expressions such as "herein incorporated by reference" or equivalents thereof (e.g. page 21, line 3) should be deleted (Guidelines, C-II, 4.18).
 - iv) The reference to unpublished documents (e.g. page 31, line 2 in the description of the present application) should either be deleted or replaced by the reference to the corresponding published document (Guidelines, C-II, 4.18).
 - v) The vague and imprecise statement in the description on page 99, line 9 in the description of the present application implies that the subject -matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims (Art. 84 EPC) when used to interpret them (Guidelines C-III, 4.3a). The statement should therefore be amended to remove this inconsistency.



Bescheid/Protokoll (Anlage)

Communication/Minutes (Annex)

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Anmelde-Nr.:
Application No.: 04 809 772.9
Demande n°:



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Patentamt

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Patent Office

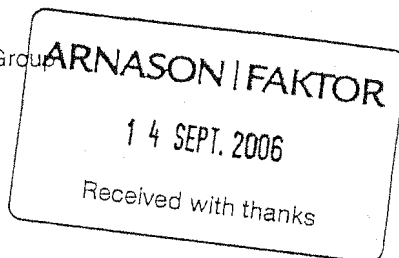
Office européen
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Application No. 04 809 772.9 - 1222	Ref. P 5541 EPPC	Date 11.09.2006
Applicant Decode Genetics EHF.		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).



Bellmann, Anja
Primary Examiner
for the Examining Division

Enclosure(s): 6 page/s reasons (Form 2906)

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Bescheid/Protokoll (Anlage)

Communication/Minutes (Annex)

Notification/Procès-verbal (Annexe)

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Date

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Anmelde-Nr.:
Application No.: 04 809 772.9
Demande n°:

The examination is being carried out on the following application documents:

Description, Pages

1-99 as published

Claims, Numbers

1-63 filed with entry into the regional phase before the EPO

Drawings, Sheets

1-90 as published

The following documents are referred to in this communication:

- D1: LUI ET AL.: "Directly Defining the Gene(s) for Genomic Disease: Use of Sequence-Integrated BAC Resource to analyse a subtle deletion/inversion involving chromosome 8p22-23.3" AMERICAN JOURNAL OF HUMAN GENETICS, AMERICAN SOCIETY OF HUMAN GENETICS, CHICAGO, IL, US, vol. 67, no. 4, SUPPL 2, October 2000 (2000-10), page 157
- D2: SUGAWARA H ET AL: "Complex low-copy repeats associated with a common polymorphic inversion at human chromosome 8p23" GENOMICS, ACADEMIC PRESS, SAN DIEGO, US, vol. 82, no. 2, August 2003 (2003-08), pages 238-244
- D3: OPHOFF ROEL A ET AL: "Genomewide linkage disequilibrium mapping of severe bipolar disorder in a population isolate." AMERICAN JOURNAL OF HUMAN GENETICS. SEP 2002, vol. 71, no. 3, September 2002 (2002-09), pages 565-574
- D4: PULVER A E: "SEARCH FOR SCHZOPHRENIA SUSCEPTIBILITY GENES"



Bescheid/Protokoll (Anlage)

Communication/Minutes (Annex)

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BIOLOGICAL PSYCHIATRY, ELSEVIER SCIENCE, NEW YORK, NY, US, vol. 47, 1 February 2000 (2000-02-01), pages 221-230

D5: WO 00/50639 A (VARIAGENICS, INC; STANTON, VINCENT, JR) 31 August 2000

D6: Hans C ET AL: "AN UNUSUAL DE NOVO INVERSION AND DUPLICATION OF CHROMOSOME 8; 46, XY, REC(8) DUP(P11 P22), INV (8)(P23 Q22) A RELATIONSHIP WITH SAN LUIS VALLEY SYNDROME?" EUROPEAN JOURNAL OF HUMAN GENETICS, KARGER, BASEL, CH, vol. 9, no. SUPPL 1, 19 May 2001 (2001-05-19), page P0266

1 Amendments (Art. 123(2) EPC)

- 1.1 The amendments filed with entry into the regional phase before the EPO do not introduce subject-matter which extends beyond the content of the application as filed, therefore these amendments comply with Article 123(2) EPC.

2 DISCLOSURE, SUPPORT AND CLARITY (Art. 83 and 84 EPC)

- 2.1 Independent claim 1 is lacking support (Article 84 EPC) and disclosure (Article 83 EPC), the reasons being the following:

- 2.1.1 It has only been shown that a number of subjects suffering from psychiatric and/or comorbid disorders present an inversion of chromosome 8p23. Experimental evidence for a direct role of the Inv8p23 genomic region in the development of psychiatric disorders is missing. From the prior art, it appears that this inversion can be linked to a number of diseases (cf. D1, D2, D3 and D4, Tab.1), but that not all carriers are suffering from said diseases nor from psychiatric disorders (cf. D2, p.241, D4, Tab.1). It has furthermore not been shown, that this inversion can be used to diagnose such disorders. **It even appears not to be possible to diagnose a psychiatric or comorbid disorder by simply analysing the orientation of inv8p23, as a number of carriers of this inversion appear to be healthy, i.e. the parents of the child, wherein the parent carrying the inv8p23 is asymptomatic, while the child showing a variety of**



Bescheid/Protokoll (Anlage)

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symptoms is bearing an additional duplication of the inv8p23 region (cf. D2, p.241, D4, Tab.1).

Therefore the subject-matter of independent claim 1 and dependent claims 2 to 13, 31 to 40, 56 and 58 does not fulfil the requirements of Article 83 and 84 EPC.

Consequently no examination will be carried out on the subject-matter of said claims.

2.2 Dependent claims 17 and 57 are unclear. They appear to refer back to the wrong claims, as these claims are defining a method, but are referring back to claim 15 and 26 respectively, which are both defining a kit (Article 84).

2.3 Dependent claims 46 to 48 and 60 to 62 are unclear. They appear to refer back to the wrong claims, as these claims are defining a method for predicting the efficacy of a drug, but are referring back to claim 40, defining a method of diagnosis and claim 41, defining a method of determining the orientation of Inv8p23 respectively (Article 84).

3 NOVELTY (Art. 54 EPC)

3.1 D1 discloses ten BAC DNA probes for detecting the orientation of the Inv8p23 genomic region and a method for determining the orientation of the Inv8p23 inversion fragment using said probes (cf. D1, abstract).

D2 discloses a complete physical map and chromosomal markers of the Inv8p23 region and a method for determining the orientation of the Inv8p23 inversion fragment using said markers (cf. D2, p.239 to 240 and p.242 to 243).

D3 and D4 disclose chromosomal markers for detecting the orientation of the Inv8p23 genomic region (cf. D3, p.569 and Tab.1 and 2, D4, p.225, col.1).

Therefore, the subject-matter of **independent claims 14 and 41 is not novel** over D1 to D4 (Article 54 EPC).

4 INVENTIVE STEP (Art. 56 EPC)

4.1 Independent claim 44:

Document D5 is considered to represent the most relevant state of the art for claim



Bescheid/Protokoll (Anlage)		Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
Datum Date Date	11.09.2006	Blatt Sheet Feuille	4
		Anmelde-Nr.: Application No.: Demande n°:	04 809 772.9

44 in its present form. D5 discloses a method of predicting the efficacy of a drug or treating a psychiatric disorder in a human patient, comprising determining the presence or absence of at least one variance in a gene (cf. cl.108).

- 4.2 The subject-matter of claim 44 differs from the subject-matter disclosed in closest prior art document D5 in that the orientation of the Inv8p23 genomic region is determined, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.
- 4.3 No unexpected technical effect appears to be associated with said difference.
- 4.4 The technical problem to be solved may therefore be regarded as providing an alternative genetic indicator for the efficacy of a drug for treating a psychiatric disorder. The proposed solution is to determine the orientation of the Inv8p23 genomic region, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.
- 4.5 This solution can be considered as involving an inventive step for the following reasons:
- 4.5.1 Even though a link between the 8p23 region and psychiatric disorders is well-known in the state of the art (cf. D1 to D6) and furthermore a link between the Inv8p23 inversion and mental retardation is known (cf. D1 and D3), so far no relationship has been established between the orientation of the inv8p23 genomic region and the efficacy of a drug for treating a psychiatric disorder.
- 4.6 Hence, the subject-matter of **independent claim 44 does involve an inventive step** (Article 56 EPC).
- 4.7 Dependent claims 15 to 30,42,43,57 and 59 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC in respect of novelty and/or inventive step, as all of the additional features fall within the scope of routine laboratory practise.

5 CONCLUSIONS



Bescheid/Protokoll (Anlage)

Communication/Minutes (Annex)

Notification/Procès-verbal (Annexe)

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Anmelde-Nr.:
Application No.: 04 809 772.9
Demande n°:

- 5.1 The Applicant is invited to file new claims which take account of the above comments.
- 5.2 In the reply, the parts of the application, as originally filed, which form the basis for the amendments (of Art 123(2) EPC) should be **clearly indicated** (page/line numbers etc).
- 5.3 In order to expedite the procedure, the Applicant is kindly asked to **clearly point out where the amendments have been made**, possibly by enclosing a copy of the original pages with the corrections in the manuscript.
- 5.4 The amendments should be filed by way of replacement pages, avoiding unnecessary recasting of the description. The Applicant should also take account of the requirements of Rule 36(1) EPC. In particular a fair copy of the amendments should be filed. If handwritten amendments are submitted, they should be clearly legible for the printer.
- 5.5 Once an allowable set of claims has been defined, then the Applicant is requested to do the following:
- i) The description should be brought into conformity with the amended claims (Rule 27(1)(c) EPC). Care should be taken during revision not to add subject-matter which extends beyond the content of the application as originally filed (Art 123(2) EPC). Any statements of problems or advantages should be restricted to the letter of reply.
 - ii) Documents **D1-D6** should be identified in the description and the relevant background art disclosed therein should be briefly discussed if the subject-matter for which these documents are relevant prior art remains in the claims (Rule 27(1)(b) EPC).
 - iii) A European patent application should be self contained. Therefore, expressions such as "herein incorporated by reference" or equivalents thereof (e.g. page **21**,



Bescheid/Protokoll (Anlage)

Communication/Minutes (Annex)

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Date

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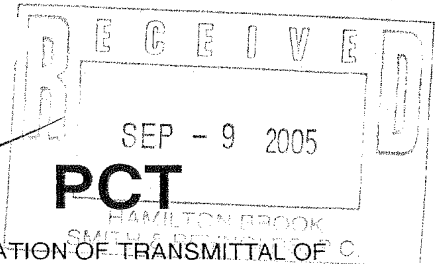
Anmelde-Nr.:
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line 3) should be deleted (Guidelines, C-II, 4.18).

- iv) The reference to unpublished documents (e.g. page 31, line 2 in the description of the present application) should either be deleted or replaced by the reference to the corresponding published document (Guidelines, C-II, 4.18).
- v) The vague and imprecise statement in the description on page 99, line 9 in the description of the present application implies that the subject -matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims (Art. 84 EPC) when used to interpret them (Guidelines C-III, 4.3a). The statement should therefore be amended to remove this inconsistency.

PATENT COOPERATION TREATY

DOCKETED



From the INTERNATIONAL SEARCHING AUTHORITY

To:

HAMILTON, BROOK, SMITH
& REYNOLDS, P.C.
Attn. Carroll, Alice O.
530 Virginia Road
P.O. Box 9133
Concord, MA 01742-9133
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference

2345.2058002

Date of mailing
(day/month/year)

12/09/2005

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2004/030699

International filing date

(day/month/year)

17/09/2004

Applicant

DECODE GENETICS EHF.

FOREIGN DOCKETING

10-12-05 SRU 12-12-05 WOF
11-12-05 WOR
12-12-05 WOF
Completed By: [Signature]

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gwenaëlle Llorca

C58

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2345.2058002	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2004/030699	International filing date (day/month/year) 17/09/2004	(Earliest) Priority Date (day/month/year) 19/09/2003
Applicant DECODE GENETICS EHF.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2004/030699

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in computer readable form
 - ☒ furnished subsequently to this Authority for the purpose of search
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/030699

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, PAJ, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	THORGEIRSSON T E ET AL: "Markers associated with the inversion polymorphism on chromosome 8p23 are associated with Panic Disorders." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 73, no. 5, November 2003 (2003-11), page 514, XP002343054 53RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HUMAN GENETICS; LOS ANGELES, CA, USA; NOVEMBER 04-08, 2003 ISSN: 0002-9297 abstract	1-63
E	WO 2005/002419 A (TRUSTEES OF BOSTON UNIVERSITY; MILUNSKY, JEFF, M) 13 January 2005 (2005-01-13) the whole document ----- -/--	1, 14, 41



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

2 September 2005

Date of mailing of the international search report

12/09/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bellmann, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LUI ET AL.: "Directly Defining the Gene(s) for Genomic Disease: Use of Sequence-Integrated BAC Recourse to analyse a subtle deletion/inversion involving chromosome 8p22-23.3" AMERICAN JOURNAL OF HUMAN GENETICS, AMERICAN SOCIETY OF HUMAN GENETICS, CHICAGO, IL, US, vol. 67, no. 4, SUPPL 2, October 2000 (2000-10), page 157, XP009047806 ISSN: 0002-9297 the whole document	14-26, 41
X	SUGAWARA H ET AL: "Complex low-copy repeats associated with a common polymorphic inversion at human chromosome 8p23" GENOMICS, ACADEMIC PRESS, SAN DIEGO, US, vol. 82, no. 2, August 2003 (2003-08), pages 238-244, XP004434191 ISSN: 0888-7543 the whole document	14-26, 41
X	OPHOFF ROEL A ET AL: "Genomewide linkage disequilibrium mapping of severe bipolar disorder in a population isolate." AMERICAN JOURNAL OF HUMAN GENETICS. SEP 2002, vol. 71, no. 3, September 2002 (2002-09), pages 565-574, XP002343055 ISSN: 0002-9297 page 569; table 1	14-26
X	PULVER A E: "SEARCH FOR SCHZOPHRENIA SUSCEPTIBILITY GENES" BIOLOGICAL PSYCHIATRY, ELSEVIER SCIENCE, NEW YORK, NY, US, vol. 47, 1 February 2000 (2000-02-01), pages 221-230, XP000944356 ISSN: 0006-3223 page 225; table 1	14-26
A	HANS C ET AL: "AN UNUSUAL DE NOVO INVERSION AND DUPLICATION OF CHROMOSOME 8; 46, XY, REC(8) DUP(P11 P22), INV (8)(P23 Q22) A RELATIONSHIP WITH SAN LUIS VALLEY SYNDROME?" EUROPEAN JOURNAL OF HUMAN GENETICS, KARGER, BASEL, CH, vol. 9, no. SUPPL 1, 19 May 2001 (2001-05-19), page P0266, XP008051011 ISSN: 1018-4813 abstract	

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>FELDMAN G L ET AL: "INVERTED DUPLICATION OF 8P: TEN NEW PATIENTS AND REVIEW OF THE LITERATURE" AMERICAN JOURNAL OF MEDICAL GENETICS, WILEY, NEW YORK, NY, US, vol. 47, no. 4, 1993, pages 482-486, XP008050996 ISSN: 0148-7299 the whole document</p> <p>-----</p>	
A	<p>MOEDJONO S J ET AL: "FAMILIAL PERICENTRIC INVERSION OF CHROMOSOME 8: IS BREAKPOINT P22Q23 IMPORTANT IN THE FORMATION OF UNBALANCED RECOMBINANTS?" ANNALES DE GENETIQUE, EXPANSION SCIENTIFIQUE FRANCAISE, PARIS, FR, vol. 23, no. 4, 1980, pages 235-237, XP008051008 ISSN: 0003-3995 the whole document</p> <p>-----</p>	
A	<p>FAN Y S ET AL: "Molecular cytogenetic characterization of a derivative chromosome 8 with an inverted duplication of 8p21.3-->p23.3 and a rearranged duplication of 8q24.13-->qter." AMERICAN JOURNAL OF MEDICAL GENETICS. 15 AUG 2001, vol. 102, no. 3, 15 August 2001 (2001-08-15), pages 266-271, XP002343056 ISSN: 0148-7299 the whole document</p> <p>-----</p>	
A	<p>GRAW S L ET AL: "Cloning, sequencing, and analysis of inv8 chromosome breakpoints associated with recombinant 8 syndrome." AMERICAN JOURNAL OF HUMAN GENETICS. MAR 2000, vol. 66, no. 3, March 2000 (2000-03), pages 1138-1144, XP002343057 ISSN: 0002-9297 the whole document</p> <p>-----</p>	
A	<p>MACINTYRE D J ET AL: "Chromosomal abnormalities and mental illness." MOLECULAR PSYCHIATRY. MAR 2003, vol. 8, no. 3, March 2003 (2003-03), pages 275-287, XP002343058 ISSN: 1359-4184 abstract; table 1</p> <p>-----</p>	
A	<p>WO 00/50639 A (VARIAGENICS, INC; STANTON, VINCENT, JR) 31 August 2000 (2000-08-31) claim 108</p> <p>-----</p>	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

The numbering of the claims does not comply with Rule 6.1(e) PCT in that some claims are numbered with non-arabic numerals, i.e. claims 13b, 26b, 34b and 43b and some claim numbers are duplicated, i.e. claims with the number 42 to 45 occur twice (Rule 6.1(b) PCT). Claims 13b, 26b, 34b and 43b were renumbered as claims 56, 57, 58 and 59 respectively and the later claims 42 to 45 were renumbered as claims 60 to 63.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/030699

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/030699

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005002419 A	13-01-2005	WO 2005002419 A2	13-01-2005
WO 0050639 A	31-08-2000	AU 3997300 A	14-09-2000
		CA 2362533 A1	31-08-2000
		EP 1224322 A2	24-07-2002
		JP 2003516111 T	13-05-2003
		WO 0050639 A2	31-08-2000
		US 2004171056 A1	02-09-2004
		US 6673908 B1	06-01-2004
		US 2001034023 A1	25-10-2001
		US 2005112680 A1	26-05-2005
		US 2002039990 A1	04-04-2002
		US 6537759 B1	25-03-2003
		US 6759200 B1	06-07-2004
		US 6664062 B1	16-12-2003

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US2004/030699

International filing date (day/month/year)
17.09.2004

Priority date (day/month/year)
19.09.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
DECODE GENETICS EHF.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Bellmann, A

Telephone No. +31 70 340-8958



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/030699

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-13,31-40,56,58 (N, IS, IA)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☒ the claims, or said claims Nos. 1-13,31-40,56,58 (N, IS, IA) are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. -
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☒ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/030699

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	44-55,60-63
	No: Claims	14-30,41-43,57,59
Inventive step (IS)	Yes: Claims	44-55,60-63
	No: Claims	14-30,41-43,57,59
Industrial applicability (IA)	Yes: Claims	14-30,41-55,57,59,60-63
	No: Claims	-

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

1 Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.1 The subject-matter of independent claim 1 does not meet the requirements of Article 5 PCT for the following reasons:

1.1.1 It has only been shown that a number of subjects suffering from psychiatric and/or comorbid disorders present an inversion of chromosome 8p23. Experimental evidence for a direct role of the inv8p23 genomic region in the development of psychiatric disorders is missing. From the prior art, it appears that this inversion can be linked to a number of diseases (cf. D1, D2, D3 and D4, Tab.1), but that not all carriers are suffering from said diseases nor from psychiatric disorders (cf. D2, p.241, D4, Tab.1). It has furthermore not been shown, that this inversion can be used to diagnose such disorders. **It even appears not to be possible to diagnose a psychiatric or comorbid disorder by simply analysing the orientation of inv8p23, as a number of carriers of this inversion appear to be healthy, i.e. the parent of the child, wherein the parent carrying the inv8p23 is asymptomatic, while the child showing a variety of symptoms is bearing an additional duplication of the inv8p23 region (cf. D2, p.241, D4, Tab.1).**

1.1.2 Therefore the subject-matter of independent claim 1 and dependent claims 2 to 13, 31 to 40, 56 and 58 does not fulfil the requirements of Article 5 PCT. consequently no examination will be carried out on the subject-matter of said claims.

2 Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are referred to in this communication:

NOVELTY (Article 33(2) PCT)

- 2.1 D1 discloses ten BAC DNA probes for detecting the orientation of the Inv8p23 genomic region and a method for determining the orientation of the Inv8p23 inversion fragment using said probes (cf. D1, abstract).
D2 discloses a complete physical map and chromosomal markers of the Inv8p23 region and a method for determining the orientation of the Inv8p23 inversion fragment using said markers (cf. D2, p.239 to 240 and p.242 to 243).
D5 and D6 disclose chromosomal markers for detecting the orientation of the Inv8p23 genomic region (cf. D5, p.225, col.1, D6, p.569 and Tab.1 and 2).
Therefore, the subject-matter of **independent claims 14 and 41 is not novel** over D1, D2, D5 and D6 (Article 33(2) PCT).

INVENTIVE STEP (Article 33(3) PCT)

- 2.2 Independent claim 44:
Document D7 is considered to represent the most relevant state of the art for claim 44 in its present form. D7 discloses a method of predicting the efficacy of a drug or treating a psychiatric disorder in a human patient, comprising determining the presence or absence of at least one variance in a gene (cf. cl.108).
- 2.3 The subject-matter of claim 44 differs from the subject-matter disclosed in closest prior art document D7 in that the orientation of the Inv8p23 genomic region is determined, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.
- 2.4 No unexpected technical effect appears to be associated with said difference.
- 2.5 The technical problem to be solved may therefore be regarded as providing an alternative genetic indicator for the efficacy of a drug for treating a psychiatric disorder. The proposed solution is to determine the orientation of the Inv8p23 genomic region, wherein the orientation of the Inv8p23 genomic region is indicative of responsiveness or non-responsiveness to the drug in the human patient.
- 2.6 This solution can be considered as involving an inventive step for the following

reasons:

- 2.6.1 Even though a link between the 8p23 region and psychiatric disorders is well-known in the state of the art (cf. D1 to D6) and furthermore a link between the Inv8p23 inversion and mental retardation is known (cf. D1 and D3), so far no relationship has been established between the orientation of the inv8p23 genomic region and the efficacy of a drug for treating a psychiatric disorder.
- 2.7 Hence, the subject-matter of **independent claim 44 does involve an inventive step** (Article 33(3) PCT).
- 2.8 Dependent claims 15 to 30,42,43,57 and 59 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, as all of the additional features fall within the scope of routine laboratory practise.

3 Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2005/002419	13.01.2005	17.06.2004	26.06.2003

Non-written disclosures

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
poster	04-08/11/2003	00/11/2003

THORGEIRSSON T E ET AL: "Markers associated with the inversion polymorphism

on chromosome 8p23 are associated with Panic Disorders." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 73, no. 5, November 2003 (2003-11), page 514, XP002343054 53RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HUMAN GENETICS; LOS ANGELES, CA, USA; NOVEMBER 04-08, 2003 ISSN: 0002-9297

4 Re Item VII

Certain defects in the international application

- 4.1 The numbering of the claims does not comply with Rule 6.1(e) PCT in that some claims are numbered with non-arabic numerals, i.e. claims 13b,26b,34b and 43b and some claim numbers are duplicated, i.e. claims with the number 42 to 45 occur twice (Rule 6.1(b) PCT).
Claims 13b,26b,34b and 43b were renumbered as claims 56, 57, 58 and 59 respectively and the later claims 42 to 45 were renumbered as claims 60 to 63.

5 Re Item VIII

Certain observations on the international application

- 5.1 Dependent claims 46 to 48 and 60 to 62 appear to refer back to the wrong claims as these claims are defining a method for predicting the efficacy of a drug but are referring back to claim 40, defining a method of diagnosis and claim 41, defining a method of determining the orientation of Inv8p23 respectively (Article 6 PCT).